

In the Application of:  
Jay M. Short  
Application No.: 09/529,458  
Filed: April 13, 2000  
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Attorney Docket No.: DIVER1380-1

# I. AMENDMENTS

## In the Claims

Please amend the claims as follows:

Sub E1  
16. (Amended) A method for identifying a DNA sequence which encodes a molecule or molecules which directly or indirectly modulate the interaction between at least a first and second molecule, comprising:

D7  
introducing into a host cell containing interacting molecules which generate or repress a detectable signal or growth of the cell, genomic DNA or clones of a DNA library generated from nucleic acid obtained from a mixed population of organisms and measuring the interaction of a first molecule and a second molecule in the presence of a third molecule encoded by the library or the genomic DNA or produced as a result of expression of one or more products encoded by the library or the genomic DNA, wherein interaction of the first and the second molecules in the absence of the third molecule produces a detectable signal or growth of the cell;

comparing the signal or growth of the cell in the presence and absence of the genomic DNA or library, wherein a difference between the response or growth is indicative of the presence of a molecule that modulates interaction between the first and second molecules; and

identifying a clone or DNA sequence which encodes a molecule or molecules which directly or indirectly modulates the interaction between the first and second molecules.

Sub E2  
D7  
23. (Amended) The method of claim 22, wherein the host cell further comprises a first recombinant gene encoding the first molecule, a second recombinant gene encoding the second molecule, or a third recombinant gene encoding the third molecule.

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D/2  
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24. (Amended) The method of claim 23, wherein the host cell contains both the first gene and the second gene and each gene is expressed.

25. (Amended) The method of claim 23, wherein the host cell contains the first, second and third genes and each gene is expressed.

E3

36. (Amended) A method for identifying a molecule that affects the interaction between a first and second molecule, comprising:

(i) contacting in a cell a first molecule with a second molecule in the presence of a third molecule encoded by a nucleic acid sequence from a library made from a mixed population of organisms or in the presence of a library or genomic DNA encoding the third molecule,

D3

wherein association of the first and second molecules in the absence of the third molecule results in the absence or presence of a detectable response by changing expression of a detectable gene or detectable gene product; and

(ii) comparing the detectable response in the presence of the third molecule with the detectable response in the absence of the third molecule, wherein a difference in response is indicative of the presence of the third molecule that affects the interaction between a first and second molecule.

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34  
E4 42. (Amended) The method of claim 36, wherein the third molecule contains a DNA binding domain and a transcriptional activation domain.

35  
E5 45. (Amended) The method of claim 36, further comprising, prior to step (i):  
obtaining an environmental sample containing a mixed population of organisms; and  
enriching the sample for prokaryotic organisms, thereby creating an enriched environmental sample.

46. (Amended) The method of claim 45, further comprising producing a normalized library, comprising :  
isolating nucleic acids from said enriched environmental sample;  
fractionating the isolated nucleic acids; and  
amplifying any single-stranded nucleic acids present in the sample.

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47. (Amended) The method of claim 46, further comprising generating an expression library, comprising:

inserting the amplified and isolated nucleic acids into an expression vector.

48. (Amended) A method for identifying a molecule that affects the interaction between a first and second molecule, comprising:

*DL*  
*ES*  
(i) contacting a first molecule with a second molecule wherein at least one of the first or second molecules is derived from a library made from a mixed population of organisms, wherein association of the first and second molecules in the presence of a third molecule results in the presence of a detectable response by changing expression of a detectable gene or detectable gene product; and

(ii) comparing the detectable response in the presence of the third molecule and the first and second molecules with the detectable response in the absence of the third molecule, wherein a difference in response is indicative of a first and second molecule that interact and a third molecule that affects the interaction between the first and second molecules and identifying the third molecule.